REMARKS

Amendments to the Specification

The paragraphs spanning lines 13-22 of page 4 and lines 4-22 of page 5 have been amended to correctly identify the clone ID associated with ATCC Deposit Number 203055. Support for these amendments may be found throughout the specification, for example, in the paragraph spanning lines 12-21 on page 15.

The paragraph spanning lines 20-27 on page 10 has been amended to correctly identify the Fas ligand polypeptide sequence shown in Figure 2. Support for this amendment is found in Figure 2 as originally filed.

The paragraphs spanning lines 8-23 on page 31, lines 8-21 on page 42 and lines 3-19 on page 49 have been amended to correct obvious typographical errors.

The paragraph spanning lines 21-36 on page 39 has been amended to include reference to SEQ ID NO:2 in two places. This amendment brings this disclosure in line with the format of the disclosure just above it and provides clarity to the reader. Further support for this amendment can be garnered from the amino acid identity of the C – terminal 150 amino acids of TNF-gamma-alpha and TNF-gamma-beta. Additionally, the description of the numbers of amino acids deleted from the N-terminus of the TNF-gamma-alpha expression constructs described in this paragraph has been amended to read "24, 38, 48, and 54" instead of "25, 39, 49, and 55". Support for this amendment lies in the knowledge that one of skill in the art would be able to properly calculate the correct numbers of amino acids deleted given the description of constructs given in this paragraph and the amino acid sequence of SEQ ID NO:2.

The paragraph on spanning lines 18-25 on page 46 has been amended to recite "tryptophan-15" instead of "tyrosine-15". Support for this amendment can be found in SEQ ID NO:2 of the Sequence Listing of the application as originally filed. Additionally, reference to "SEQ IN NO:2" was corrected to "SEQ ID NO:2"

Each of these amendments is fully supported by the specification as filed and no new matter has been introduced.

Amendments to the Claims

Amendments to claims 42, 51, 55, 65, 75, and 89 are discussed in the section addressing the Examiner's rejections of the claims 35 U.S.C. §112, first paragraph.

Substitute Sequence Listing

The Substitute Sequence Listing submitted herewith has been amended to bring the Sequence Listing into agreement with the specification and the drawings and to bring the Sequence Listing into compliance with the 37 C.F.R. §1.821- §1.825. Briefly the amendments to the Sequence Listing include: (a) amendment of the header information to correctly represent the filing date of the present application; (b) amendments to SEQ ID NOS: 3, 4, and 6 to make the Sequence Listing correctly reflect the sequences shown in Figure 2; (c) amendments of the features listings of SEQ ID NOS:9, 10, 12, 22, and 23 have been amended to properly reflect the position of the "n" nucleotides; and (d) amendment of the definition of "n" nucleotide to include the inadvertently omitted nucleotide "c" in the features listings of SEQ ID NO:10. Amendment (d) above is supported by the general recognition in the art of the definition of "n" nucleotides as including all a, c, g, and t and in the fact that Applicants correctly defined 'n' nucleotides in every other sequence in the Sequence Listing. Each of the amendments is supported by the specification as originally filed or by the knowledge of one skilled in the art, and no new matter has been introduced.

Response to rejections of the claims under 35 U.S.C. §112, first paragraph

The Examiner has maintained rejections of claims 42 and 49-94 under 35 U.S.C. § 112, first paragraph as set forth in the Office Action mailed July, 13, 2000 at item 4.

To summarize:

In the July, 13, 2000 Office Action (Prosecution Paper No. 8), Examiner Draper states that specification has not enabled claims directed to (a) polypeptide fragments that have TNF-gamma-alpha activity; (b) to polypeptides encoded by nucleotide sequences encoding at least 10 contiguous amino acids of TNF-gamma-alpha, or polypeptides comprising at least 30 contiguous amino acids of TNF-gamma-alpha; (c) TNF-gamma-alpha fragments that bind an antibody specific for TNF-gamma-alpha; and (d) to heterologous polypeptide sequences linked to TNF-gamma-alpha polypeptide sequences.

Applicants strongly disagree with this rejection for the reasons provided in the Response and Amendment filed January 16, 2001, and not wishing to overburden the prosecution history, Applicants will primarily address those issues relevant to the reasons the Examiner has provided for maintaining this rejection.

The Examiner rejected claims that require a polypeptide or fragment to have "TNF-gamma-alpha activity" under 35 U.S.C. § 112, first paragraph because the phrase "'TNF-gamma-alpha activity' encompasses any and all conceivable activities, including those that are not described in the instant specification, whereas the specification only provides for inhibition of angiogenesis." (see, page 4, lines 9-11 of Paper No. 15). Applicants strongly disagree with the Examiner's assertions, particularly with the statement that the application only provides for the inhibition of angiogenesis. TNF-gamma-alpha polypeptides as well as anti-TNF-gamma-alpha antibodies, as just one example, are useful in the treatment and diagnosis of inflammation, infectious diseases and tumors. (See, for example, page 8, lines 25-31). Nevertheless, in the interest of facilitating prosecution, Applicants have amended claim 42 so as to delete the phrase "TNF-gamma-alpha activity" and have cancelled claims reciting the "TNF-gamma-alpha activity" limitation (i.e., claims 50, 57, 60, 67, 70, 78, 81, and 90). Accordingly, this aspect of the rejection has been obviated and Applicants respectfully request that this aspect of the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

The Examiner rejected claims that require a polypeptide or fragment thereof to bind an antibody specific for TNF-gamma-alpha under 35 U.S.C. § 112, first paragraph for the following reasons: (a) because "[a]n artisan cannot determine what additional limitations are placed upon a claim by the presence of this term;" (b) because the claims do not require that the antibody binding be to the "single exemplified species;" and (c) because "the claims do not appear to require the same specificity of interaction between the antibodies and a 'TNF-gamma-alpha polypeptide'...and a claimed polypeptide or fragment...;" (See page 3, line 5 to page 4, line 7 of Paper No. 15).

Applicants have amended claims 42, 55, 65, 75, and 89 such that the antibody must be specific for the polypeptide of SEQ ID NO:2 and specifically bind the claimed polypeptide or fragment thereof. These amendments obviate Examiner's arguments (b) and (c).

Applicants also note that contrary to the Examiner's definition, a "specific" antibody is not one that binds only one polypeptide to the exclusion of all others. Instead, the art understood meaning of the concept of antibody "specificity" allows for an antibody to bind more than one polypeptide. In support of this point, Applicants note that numerous antigen specific antibodies are commercially available which bind more than a single

polypeptide species. As just one of many available examples, Boehringer Manheim, Inc. sells an anti-L-CAM/Uvomorulin (clone 6F9) antibody which is described in the catalog as an "antibody [that] *specifically* recognizes the 120 kD and the 80 kD band of L-CAM/Uvomorulin (Arc-1 E-cadherin cell-CAM 120/80) in man and rabbit." (*See,* Boehringer Mannheim Biochemicals, Inc. 1994 Catalog, pp. 280-1, attached hereto as Appendix A). This example makes it clear that within the art at the time of filing a specific antibody may bind more than one polypeptide and that these polypeptides may even be from different species.

Further, Applicants respectfully disagree with the Examiner's contention that an "artisan cannot determine what additional limitations are placed upon a claim" by the presence of the requirement that the claimed polypeptide must specifically bind a polypeptide that specifically binds the polypeptide of SEQ ID NO:2. (See, page 3, lines 5-8 of paper No. 15). More specifcally, the Examiner appears to object to the fact that an artisan must perform some experimentation in order to determine the scope of the claims.

It is well settled that the test for enablement is whether one reasonably skilled in the art could make and use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics, Inc.,* 857 F.2d 778, 8 U.S.P.Q. 2d 1217 (Fed. Cir. 1988). Under 35 U.S.C. § 112, an inventor is not required to disclose "a test of every species encompassed by their claims,"even in an unpredictable art. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976) (emphasis in original). Enablement is not precluded even if some experimentation is necessary. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1376, 1384 (Fed. Cir. 1986). This is so even if the amount of experimentation required is laborious. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

Applicants assert that the art of making antibodies that specifically bind the polypeptide of SEQ ID NO:2 is routine within the relevant arts, as is the testing of such antibodies' abilities to bind polypeptides with sequences that are related to SEQ ID NO:2. Thus, while it may be laborious to produce the antibodies and polypeptides and to test their abilities' to bind one another, such work does not fall within the realm of "undue experimentation." Furthermore because making antibodies and testing their specificity is routine within the art, it must follow that one of ordinary skill in the art is fully able to comprehend the limitations placed upon the claimed polypeptides by the presence of the

requirement that they specifically bind an antibody that specifically binds the polypeptide of SEQ ID NO:2.

In light of the foregoing, Applicants respectfully request that this aspect of the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

The Examiner has additionally rejected claims directed to polypeptides "having a recited % identity with SEQ ID NO:2 wherein the polypeptide is functionally unlimited" under 35 U.S.C. §112, first paragraph because "the specification has not told the skilled artisan how to use a polypeptide that does not have a specific activity instantly disclosed..." (See page 5, lines 12-15 of Paper No. 15). Applicants have amended claim 75 such that the claimed polypeptide that is 90% or more identical to all or a portion of SEQ ID NO:2 must specifically bind an antibody that specifically binds the polypeptide of SEQ ID NO:2. The Examiner appears to contend that such limitation of the claimed polypeptide is insufficient because the ability to specifically bind an antibody that specifically binds the polypeptide of SEQ ID NO:2 does not correlate with "TNF-gamma-alpha activity" and that "TNF-gamma-alpha activity is an omitted, but essential, element of such a claim.

Applicants respectfully disagree. Under 35 U.S.C. § 112, the specification need only enable a person of ordinary skill in the art to make the claimed polypeptides and practice *a single* use of the claimed polypeptides without undue experimentation. Applicants assert that the claimed polypeptides need not have biological activity in terms of TNF-gamma alpha activity in order to be useful. The claimed polypeptides may be used, for example, to generate an antibody that is specific for SEQ ID NO:2. Applicants are aware that the Examiner contends that a

> "skilled artisan would not employ a polypeptide containing an unlimited plurality of epitopes to make antibodies specific for the exemplified polypeptide [SEQ ID NO:2], nor would the artisan employ such polypeptides for related purposes, e.g., specific detection of the presence of antibodies to the exemplified polypeptide." (See page 5, lines 4-8, of Paper No. 15.)

and respectfully disagree.

Applicants point out that the Examiner has applied an improper legal standard in maintaining this rejection. The relevant inquiry for enablement of the claims at issue is not whether one skilled in the art would be inclined to use a polypeptide species falling

within the scope of the claimed genus as a to generate an anti-TNF-gamma-alpha antibody; but rather, as Judge Rich explained in *In re Vaeck*, 20 USPQ2d 1438, 1445 (Fed.Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to *determine*, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility" (emphasis provided). See *In re Angstadt*, 537 F.2d 498, 502-503, 190, U.S.P.Q. 214, 218 (C.C.P.A. 1976):

> To require such a complete disclosure would apparently necessitate a patent with "thousands of examples . . . More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments . . .

Applicants assert that it would be routine for one of ordinary skill in the relevant arts to generate antibodies that bind polypeptides encoded by the claimed polynucleotides using, for example, phage display technology combined with guidance from the specification regarding the primary sequence of the polypeptide and predicted epitopes. (See, e.g., page 48, line 16 through page 52, line 24 of the specification). Applicants submit that, since the disclosed or otherwise known methods of making and screening the claimed polypeptides may be used to *determine*, without undue experimentation, whether a given polypeptide comprising a TNF gamma polypeptide fragment demonstrates a disclosed utility (e.g., to encode a polypeptide that binds an antibody to TNF-gamma-alpha, or use in the generation of anti-TNF-gamma-alpha antibodies), the enablement requirement is fully satisfied. *In re Wands*, 858 F.2d at 738, 8 U.S.P.Q.2d at 1404; *Ex parte Mark*, 12 U.S.P.Q.2d 1904, 1906-1907 (B.P.A.I. 1989).

Furthermore, Applicants respectfully submit that the Examiner is in error, and that there are countless examples in the literature of skilled artisans using a small portion of a "polypeptide X" in association with a much larger heterologous protein or entity to make an antibody that binds polypeptide X. It is a common practice to couple a small portion of polypeptide X to a much larger carrier protein such as keyhole limpet hemocyanin (KLH) to induce antibodies specific for polypeptide X. In the same vein, it is not an uncommon practice to generate fusion or chimeric proteins containing a small portion of polypeptide X to generate antibodies specific for polypeptide X. Nor is it uncommon immunize with the fusion/chimeric protein expressed on the surface of a bacterial cell, mammalian cell, or virus particle where the portion of polypeptide X is an even smaller percentage of the total

available epitopes in the immunogen. Applicants would like to note that such fusion proteins are generated by fusion of heterologous polynucleotide sequences, followed by expression of the fusion protein, which is then used to generate antibodies, which is precisely the utility Applicants have asserted. Applicants submit herewith copies of O'Rand et al., Journal of Reproductive Immunology (1993) 25:89-92 and Charbit et al., Vaccine (1993) 11:1221-8 in support of these assertions (See Appendix B).

Applicants submit that a skilled artisan would indeed know how to use a polypeptide having a recited % identity to all or a portion of SEQ ID NO:2. Thus, Applicants respectfully request that this aspect of the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

The Examiner has also rejected claims directed to a polypeptide encoded by a polynucleotide that hybridizes to the open reading frame of SEQ ID NO:1 under 35 U.S.C. § 112 "because a certain degree of similarity at the nucleotide level does not imply like similarity at the amino acid level..." (See page 6, lines 4-6 of Paper No. 15).

Applicants have amended claim 89 such that it recites that the claimed polypeptide encoded by a polynucleotide that hybridizes to complement of the open reading frame of SEQ ID NO:1 must specifically bind an antibody that specifically binds the polypeptide of SEQ ID NO:2. This claim limitation ensures that the claimed polypeptide has structural similarity with the polypeptide of SEQ ID NO:2, thus addressing the Examiner's concerns. As above, these polypeptides are useful, for example, to generate an antibody against the polypeptide of SEQ ID NO:2. Accordingly, Applicants respectfully request that this aspect of the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

Conclusion

Applicants respectfully request that the amendments and remarks of the present reply be entered and made of record in the present application. Applicants believe that each ground of rejection has been successfully overcome or obviated and that the claims are now in condition for allowance. Withdrawal of all of the Examiner's rejections and objections and allowance of the application is earnestly requested. An early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number

provided below if any further action by Applicants would expedite the examination of this application.

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date: September 26, 2001

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Enclosures
KKH/MS/cmp

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Yu et al.	Art Unit:	1647
Application Serial No.:	09/246,129	Examiner:	Romeo, D.
Filed:	February 8, 1999	Atty Docket No.:	PF141P4

For: **TUMOR NECROSIS FACTOR-GAMMA**

OIPE JC147 SEP 26 2001 PATENT & TRADEMARK OFFICE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Amendments are shown in bold with insertions indicated with underlining and deletions indicated by strikeout.

In the Specification:

Applicants have requested that the paragraph spanning lines 13-22 of page 4 be amended as follows:

The present invention also provides isolated nucleic acid molecules comprising a polynucleotide encoding at least a portion of the TNF-gamma-beta polypeptide having the complete amino acid sequence shown in SEQ ID NO:20 or the complete amino acid sequence encoded by the cDNA clone ~~**HEMCZ51**~~ **HEMCZ56** deposited as plasmid DNA as ATCC Deposit Number 203055 on July 9, 1998. The nucleotide sequence determined by sequencing the deposited TNF-gamma-beta clone, which is shown in Figures 20A and B (SEQ ID NO:20), contains an open reading frame encoding a complete polypeptide of 251 amino acid residues, including an initiation codon encoding an N-terminal methionine at nucleotide positions 1-3, and a predicted molecular weight of about 28,089 Da.

Applicants have requested that the paragraph spanning lines 4-22 of page 5 be amended as follows:

In another embodiment, the invention provides an isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence selected from the group consisting of: (a) a nucleotide sequence encoding the TNF-gamma-beta polypeptide having the complete amino acid sequence in SEQ ID NO:20 (i.e., positions 1 to 251 of SEQ ID NO:20); (b) a nucleotide sequence encoding the TNF-gamma-beta polypeptide having the complete amino acid sequence in SEQ ID NO:20 excepting the N-terminal methionine (i.e., positions 2 to 251 of SEQ ID NO:20); (c) a nucleotide sequence encoding the mature TNF-gamma-beta polypeptide having the amino acid sequence in SEQ ID NO:20 shown as positions 62 to 251 of SEQ ID NO:20; (d) a nucleotide sequence encoding the TNF-gamma-beta polypeptide having the complete amino acid encoded by the cDNA clone ~~HUVEO91~~ HEMCZ56 contained in ATCC Deposit No. 203055; (e) a nucleotide sequence encoding the TNF-gamma-alpha polypeptide having the complete amino acid sequence excepting the N-terminal methionine encoded by the cDNA clone ~~HUVEO91~~ HEMCZ56 contained in ATCC Deposit No. 203055; (f) a nucleotide sequence encoding the mature TNF-gamma-beta polypeptide having the amino acid sequence encoded by the cDNA clone ~~HUVEO91~~ HEMCZ56 contained in ATCC Deposit No. 203055; and (g) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e) or (f), above.

Applicants have requested that the paragraph spanning lines 20-27 on page 10 be amended as follows:

Figures 2A-C illustrate an amino acid sequence alignment between TNF-gamma-alpha (SEQ ID NO:2) and other members of the TNF family including human TNF-alpha (GenBank No. Z15026; SEQ ID NO:3), human TNF-beta (GenBank No. Z15026; SEQ ID NO:4), human lymphotoxin-beta (LTbeta; GenBank No. L11016; SEQ ID NO:5), and ~~human~~ rat Fas Ligand (FASL: GenBank No. ~~U11821~~U034070; SEQ ID NO:6). TNF-gamma contains the conserved amino acid residues of the TNF family as shown by the

boxed and shaded areas. The aligned molecules are presented in their entirety as Figures 2A, 2B, and 2C.

Applicants have requested that the paragraph spanning lines 8-23 on page 31 be amended as follows:

Preferred, however, are nucleic acid molecules having sequences at least 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequence shown in Figures 1A and B (SEQ ID NO:1), Figures 20A and B (SEQ ID NO:19), or to the nucleic acid sequence of the deposited cDNA clones, or fragments thereof, which do, in fact, encode a polypeptide having ~~TNT-gamma~~ **TNF-gamma** functional activity. By "a polypeptide having TNF-gamma functional activity" is intended polypeptides exhibiting activity similar, but not necessarily identical, to an activity of the TNF-gamma polypeptide of the invention (either the full-length protein or, preferably, the mature protein), as measured in a particular immunoassay and/or biological assay. For example, TNF-gamma activity can be measured using an apoptosis assay as described in Example 7, by determining the relative ability of TNF-gamma to inhibit the FGF-2-induced formation of capillary-like tubular structure formation in cultures of ABAE cells as described in detail in Example 9 or in a chorioallantoic membrane (CAM) angiogenesis assay as described in Example 10, by its effect(s) on the activation of cellular NF-κB and c-Jun kinase (JNK) as described in Example 12, and in several additional ways described in the remaining Examples and in the art.

Applicants have requested that the paragraph spanning lines 21-36 on page 39 be amended as follows:

The remaining TNF-gamma-alpha expression constructs were used to express various TNF-gamma muteins from bacterial, baculoviral, and mammalian systems. Four N-terminal deletion mutations have been generated using the pQE60 bacterial expression vector. These N-terminal deletion mutation constructs are: (i) pQE60TNFg-3/147 (representing a possible mature TNF-gamma polypeptide; the polypeptide expressed by this construct is identical to amino acid residues 107-251 of the TNF-gamma-beta of SEQ ID NO:20), (ii) pQE60TNFg12/147 (representing amino acid residues 12-147 of SEQ ID

NO:2 and residues 116-251 of SEQ ID NO:20), (iii) pQE60TNFg22/147 (representing amino acid residues 22-147 **of SEQ ID NO:2** and residues 126-251 of SEQ ID NO:20), and (iv) pQE60TNFg28/147 (representing amino acid residues 28-147 **of SEQ ID NO:2** and residues 132-251 of SEQ ID NO:20). Each of these expression constructs can be used to produce a TNF-gamma polypeptide in a bacterial system which exhibits an N-terminal deletion of ~~25, 39, 49, and 55~~ **24, 38, 48 and 54** amino acids, respectively, with regard to the full-length TNF-gamma-alpha polypeptide or an N-terminal deletion of 106, 115, 125, and 131 amino acids, respectively, with regard to the full-length TNF-gamma-beta polypeptide.

Applicants have requested that the paragraph spanning lines 8-21 on page 42 be amended as follows:

The terms "fragment," "derivative" and "analog" when referring to the polypeptides of Figures 1A and 1B or Figures 20A and 20B, and those polypeptodes encoded by the deposited cDNAs, means a polypeptide which retains a TNF-gamma functional activity, i.e,. displays one or more functional activities associated with a full-length and/or mature TNF-gamma polypeptide disclosed in Figures 1A and B (SEQ ID NO:2), Figures 20 A and B (SEQ ID NO:20), and/or ~~encloded~~ **encoded** by one or both of the deposited clones (HUVEO91 and HEMCZ56). As one example, such fragments, derivatives, or analogs, which have the desired immunogenicity or antigenicity can be used, for example, in immunoassays, for immunization, for inhibition of TNF-gamma activity, etc. Thus, a specific embodiment of the invention relates to a TNF-gamma fragment that can be bound by an antibody that specifically binds the TNF-gamma polypeptide sequence disclosed in Figures 1A and B (SEQ ID NO:2), Figures 20 A and B (SEQ ID NO:20)), and/or which is encloded by one or both of the deposited clones (HUVEO91 and HEMCZ56).

Applicants have requested that the paragraph spanning lines 3-19 on page 49 be amended as follows:

Antigenic epitope-bearing peptides and polypeptides of the invention preferably contain a sequence of at least seven, more preferably at least nine and most preferably between about 15 to about 30 amino acids contained within the amino acid sequence of a polypeptide of the invention. Non-limiting examples of antigenic polypeptides or peptides that can be used to generate TNF-gamma-specific antibodies include: a polypeptide comprising amino acid residues from about Thr-24 to about Asn-32 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about Ile-37 to about Ile-45 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about Met-54 to about Arg-62 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about Gln-63 to about Asp-71 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about Glu-57 to about Gly-65 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about Val-80 to about Thr-88 in SEQ ID NO:2; a polypeptide comprising amino acid residues from about Leu-116 to about Val-124 in SEQ ID NO:2; and a polypeptide comprising amino acid residues from about Asp-133 to about Phe-141 in SEQ ID NO:2. These polypeptide fragments have been determined to bear antigenic epitopes of the TNF-gamma protein by the analysis of the Jameson-Wolf **antigenic** ~~**antigeme**~~ index, as shown in Figure 17, above.

Applicants have requested that the paragraph spanning lines 18-25 on page 46 be amended as follows:

Several amino acids of the TNF-gamma polypeptide are highly conserved across the known members of the TNF-related protein family. By making a specific mutation in TNF-gamma in such residues as ~~**tyrosine-15**~~ **tryptophan-15** (as numbered in SEQ ~~**IN**~~ **ID** NO:2), leucine-35, glycine-41, tyrosine-43, tyrosine-46, glutamine-48, leucine-90, leucine-116, glycine-119, aspartic acid-120, phenylalanine-141, phenylalanine-142, and leucine-147, it is likely that an noticeable effect on biological activity will be observed. These identical amino acid residues are, of course, present in the corresponding positions of TNF-gamma-beta shown in SEQ ID NO:20.

In the Claims:

Claims 49, 50, 57, 58, 60, 61, 67 68, 70, 71, 78, 79, 81, 82, 90 and 91 have been cancelled without prejudice.

Claims 42, 51, 55, 65, 75, and 89 have been amended as follows:

42. (Once Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) amino acid residue -27 to amino acid residue +147 as set forth in SEQ ID NO:2;

(b) amino acid residue -26 to amino acid residue +147 as set forth in SEQ ID NO:2;

(c) amino acid residue +1 to amino acid residue +147 as set forth in SEQ ID NO:2;

(d) a fragment of the polypeptide of SEQ ID NO:2, wherein the fragment **specifically binds an antibody that specifically binds the polypeptide of SEQ ID NO:2** ~~**has TNF-gamma-alpha activity**~~;

(e) a full-length polypeptide having the amino acid sequence expressed by the cDNA plasmid contained in ATCC Deposit No. 75927;

(f) a full-length polypeptide, excluding the N-terminal methionine residue, having the amino acid sequence expressed by the cDNA plasmid contained in ATCC Deposit No. 75927;

(g) a mature polypeptide having the amino acid sequence expressed by the cDNA plasmid contained in ATCC Deposit No. 75927; and

(h) a fragment of the polypeptide having the amino acid sequence expressed by the cDNA plasmid contained in ATCC Deposit No. 75927, wherein the

fragment **specifically binds an antibody that specifically binds the polypeptide of SEQ ID NO:2** ~~has TNF-gamma-alpha activity~~.

51. (Once Amended) The isolated polypeptide of claim **42** ~~49~~ wherein said fragment binds an antibody specific for TNF-gamma-alpha.

55. (Twice Amended) An isolated polypeptide encoded by a nucleic acid molecule comprising a polynucleotide sequence selected from the group consisting of:

(a) a polynucleotide sequence of at least 30 contiguous nucleotides of nucleotides 783 to 1304 of SEQ ID NO:1;

(b) a polynucleotide sequence of at least 30 contiguous nucleotides of the open reading frame encoded by the cDNA plasmid contained in ATCC Deposit No. 75927; ~~.~~

wherein said polypeptide specifically binds an antibody that specifically binds the polypeptide of SEQ ID NO:2.

65. (Once Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) an amino acid sequence comprising at least 30 contiguous amino acid residues of SEQ ID NO:2; and

(b) an amino acid sequence comprising at least 30 contiguous amino acid residues encoded by the cDNA plasmid contained in ATCC Deposit No. 75927; ~~.~~

wherein said polypeptide specifically binds an antibody that specifically binds the polypeptide of SEQ ID NO:2.

75. (Twice Amended) An isolated polypeptide comprising a first amino acid sequence 90% or more identical to a second amino acid sequence selected from the group consisting of:

(a) a second amino acid sequence comprising amino acid residues -27 to 147 of SEQ ID NO:2;

(b) a second amino acid sequence comprising amino acid residues -26 to 147 of SEQ ID NO:2; and

(c) a second amino acid sequence comprising amino acid residues 1 to 147 of SEQ ID NO:2; ~~.~~

wherein said polypeptide specifically binds an antibody that specifically binds the polypeptide of SEQ ID NO:2.

89. (Twice Amended) An isolated polypeptide encoded by a nucleic acid molecule comprising a polynucleotide which hybridizes to the complement of the polynucleotide set forth in nucleotides 783 to 1304 of SEQ ID NO:1 wherein said hybridization occurs under conditions comprising hybridization in a buffer consisting of 50% formamide, 5x SSC, 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA at 42°C and wash in a solution consisting of 0.1x SSC at 65°C, **wherein said polypeptide specifically binds an antibody that specifically binds the polypeptide of SEQ ID NO:2**.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Yu et al.	Art Unit:	1647
Application Serial No.:	09/246,129	Examiner:	Romeo, D.
Filed:	February 8, 1999	Atty Docket No.:	PF141P4

For: **TUMOR NECROSIS FACTOR-GAMMA**

CLEAN VERSION OF THE ENTIRE SET OF PENDING CLAIMS

42. (Once Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) amino acid residue -27 to amino acid residue +147 as set forth in SEQ ID NO:2;

(b) amino acid residue -26 to amino acid residue +147 as set forth in SEQ ID NO:2;

(c) amino acid residue +1 to amino acid residue +147 as set forth in SEQ ID NO:2;

(d) a fragment of the polypeptide of SEQ ID NO:2, wherein the fragment specifically binds an antibody that specifically binds the polypeptide of SEQ ID NO:2;

(e) a full-length polypeptide having the amino acid sequence expressed by the cDNA plasmid contained in ATCC Deposit No. 75927;

(f) a full-length polypeptide, excluding the N-terminal methionine residue, having the amino acid sequence expressed by the cDNA plasmid contained in ATCC Deposit No. 75927;

(g) a mature polypeptide having the amino acid sequence expressed by the cDNA plasmid contained in ATCC Deposit No. 75927; and

(h) a fragment of the polypeptide having the amino acid sequence expressed by the cDNA plasmid contained in ATCC Deposit No. 75927, wherein the fragment specifically binds an antibody that specifically binds the polypeptide of SEQ ID NO:2.

43. (New) The isolated polypeptide of claim 42 comprising amino acid residue -27 to amino acid residue +147 as set forth in SEQ ID NO:2.

44. (New) The isolated polypeptide of claim 42 comprising amino acid residue -26 to amino acid residue +147 as set forth in SEQ ID NO:2.

45. (New) The isolated polypeptide of claim 42 comprising amino acid residue +1 to amino acid residue +147 as set forth in SEQ ID NO:2.

46. (New) The isolated polypeptide of claim 42 comprising a full-length polypeptide having the amino acid sequence expressed by the human cDNA contained in ATCC Deposit No. 75927.

47. (New) The isolated polypeptide of claim 42 comprising a full-length polypeptide, excluding the N-terminal methionine residue, having the amino acid sequence expressed by the human cDNA contained in ATCC Deposit No. 75927.

48. (New) The isolated polypeptide of claim 42 comprising a mature polypeptide having the amino acid sequence expressed by the human cDNA contained in ATCC Deposit No. 75927.

51. (Once Amended) The isolated polypeptide of claim 42 wherein said fragment binds an antibody specific for TNF-gamma-alpha.

52. (New) The isolated polypeptide of claim 42 wherein said polypeptide further comprises a heterologous polypeptide.

53. (New) The isolated polypeptide of claim 52 wherein said heterologous polypeptide is the Fc domain of immunoglobulin.

54. (New) A composition comprising the polypeptide of claim 42 and a pharmaceutically acceptable carrier.

55. (Twice Amended) An isolated polypeptide encoded by a nucleic acid molecule comprising a polynucleotide sequence selected from the group consisting of:

(a) a polynucleotide sequence of at least 30 contiguous nucleotides of nucleotides 783 to 1304 of SEQ ID NO:1;

(b) a polynucleotide sequence of at least 30 contiguous nucleotides of the open reading frame encoded by the cDNA plasmid contained in ATCC Deposit No. 75927;

wherein said polypeptide specifically binds an antibody that specifically binds the polypeptide of SEQ ID NO:2.

56. (New) The isolated polypeptide of claim 55 which comprises (a).

59. (New) The isolated polypeptide of claim 55 which comprises (b).

62. (New) The isolated polypeptide of claim 55 wherein said polypeptide further comprises a heterologous polypeptide.

63. (New) The isolated polypeptide of claim 62 wherein said heterologous polypeptide is the Fc domain of immunoglobulin.

64. (New) A composition comprising the polypeptide of claim 55 and a pharmaceutically acceptable carrier.

65. (Once Amended) An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) an amino acid sequence comprising at least 30 contiguous amino acid residues of SEQ ID NO:2; and

(b) an amino acid sequence comprising at least 30 contiguous amino acid residues encoded by the cDNA plasmid contained in ATCC Deposit No. 75927; wherein said polypeptide specifically binds an antibody that specifically binds the polypeptide of SEQ ID NO:2.

66. (New) The isolated polypeptide of claim 65 which comprises (a).

69. (New) The isolated polypeptide of claim 65 which comprises (b).

72. (New) The isolated polypeptide of claim 65 wherein said polypeptide further comprises a heterologous polypeptide.

73. (New) The isolated polypeptide of claim 72 wherein said heterologous polypeptide is the Fc domain of immunoglobulin.

74. (New) A composition comprising the polypeptide of claim 65 and a pharmaceutically acceptable carrier.

75. (Twice Amended) An isolated polypeptide comprising a first amino acid sequence 90% or more identical to a second amino acid sequence selected from the group consisting of:

(a) a second amino acid sequence comprising amino acid residues -27 to 147 of SEQ ID NO:2;

(b) a second amino acid sequence comprising amino acid residues -26 to 147 of SEQ ID NO:2; and

(c) a second amino acid sequence comprising amino acid residues 1 to 147 of SEQ ID NO:2;

wherein said polypeptide specifically binds an antibody that specifically binds the polypeptide of SEQ ID NO:2.

76. (New) The isolated polypeptide of claim 75 wherein said first amino acid sequence is 95% or more identical to said second amino acid sequence.

77. (New) The isolated polypeptide of claim 75 which comprises second amino acid sequence (a).

80. (New) The isolated polypeptide of claim 75 which comprises second amino acid sequence (b).

83. (New) The isolated polypeptide of claim 75 which comprises second amino acid sequence (c).

84. (New) The isolated polypeptide of claim 83 wherein said polypeptide has TNF-gamma-alpha activity.

85. (New) The isolated polypeptide of claim 83 wherein said polypeptide binds an antibody specific for TNF-gamma-alpha.

86. (New) The isolated polypeptide of claim 75 wherein said polypeptide further comprises a heterologous polypeptide.

87. (New) The isolated polypeptide of claim 86 wherein said heterologous polypeptide is the Fc domain of immunoglobulin.

88. (New) A composition comprising the polypeptide of claim 75 and a pharmaceutically acceptable carrier.

89. (Twice Amended) An isolated polypeptide encoded by a nucleic acid molecule comprising a polynucleotide which hybridizes to the complement of the polynucleotide set forth in nucleotides 783 to 1304 of SEQ ID NO:1 wherein said hybridization occurs under conditions comprising hybridization in a buffer consisting of 50% formamide, 5x SSC, 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA at 42°C and wash in a solution consisting of 0.1x SSC at 65°C, wherein said polypeptide specifically binds an antibody that specifically binds the polypeptide of SEQ ID NO:2.

92. (New) The isolated polypeptide of claim 89 wherein said polypeptide further comprises a heterologous polypeptide.

93. (New) The isolated polypeptide of claim 92 wherein said heterologous polypeptide is the Fc domain of immunoglobulin.

94. (New) A composition comprising the polypeptide of claim 89 and a pharmaceutically acceptable carrier.